IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Martha G. Welch et al.	Confirmation No.:	8041
Application No.:	10/799,941	Art Unit:	1654
Filed:	March 11, 2004	Examiner:	Andrew D. Kosar
Title:	NOVEL MULTIPEPTIDE REGIMEN FOR THE TREATMENT OF AUTISTIC SPECTRUM, BEHAVIORAL, EMOTIONAL AND VISCERAL INFLAMMATION/AUTOIMMUNE DISORDERS		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.131

We, Martha G. Welch, David A. Ruggiero, and Muhammad Anwar, hereby declare as follows:

1. We are the inventors of the subject matter claimed in the above-identified patent application.

2. The invention claimed in the patent application was made in the United States.

3. The work described in this Declaration was performed by us, or on our behalf under our direction.

4. We declare that the pharmaceutical composition of present claim 1, as recited below, was reduced to practice by us at least prior to October 3, 2002.

5. Claim 1: A pharmaceutical composition comprising a therapeutically effective amount of a combination of secretin and oxytocin.

6. Exhibits A-C, the contents of which are described below, provide evidence of the reduction to practice of a pharmaceutical composition comprising a therapeutically effective amount of a combination of secretin and oxytocin prior to October 3, 2002.

7. **Exhibit A** shows that a composition comprising a therapeutically effective amount of a combination of secretin and oxytocin was administered to rats prior to October 3, 2002. The first page of Exhibit A is a copy of a laboratory notebook page describing experiment "CP-63." In this experiment inflammatory bowel disease "IBD" was induced by treatment of some of the rats with trinitrobenzene sulfonic acid (TNBS). As illustrated on the first page of Exhibit A, a composition comprising 0.42 μg/99μl of oxytocin ("oxy") in combination with 0.42 μg/99μl of secretin ("sec") was administered to two rats (animal number 2 - "control" and animal number 3 - "IBD"). The date on which this composition was administered, which has been redacted from the Exhibit, was prior to October 3, 2002. The second page of Exhibit A shows that the combination of secretin and oxytocin administered in experiment CP-63 was therapeutically effective. It can been seen that there was a markedly higher level of C-fos immunoreactivity in the cingulate gyrus following induction of IBD (see the higer amount dark immunostaining in the "IBD experimental" slide as compared to the "IBD control" slide). It can also be seen that the amount of C-fos immunoreactivity in the cingulate gyrus was markedly lower in IBD rats that had been treated with a combination of secretin and oxytocin (see the lower amount dark immunostaining in the "IBD – Secretin Oxytocin Injected" slide as compared to the "IBD - experimental" slide). As described in multiple locations in the above identified patent application, C-fos expression is a marker of the colitis-induced stress reaction.

8. **Exhibit B** shows an additional experiment in which a composition comprising a therapeutically effective amount of a combination of secretin and oxytocin was administered to rats prior to October 3, 2002. The first page of Exhibit B is a copy of a laboratory notebook page describing experiment "CP-76." In this experiment IBD was induced by treatment of some of the rats with TNBS. As illustrated on the first page of Exhibit B, a composition comprising a combination of oxytocin ("oxy") and secretin ("sec") was administered to two rats (see the arrow indicating "pair 1 sec + oxy"). The

date on which this composition was administered, which has been redacted from the Exhibit, was prior to October 3, 2002. The second page of Exhibit B shows that the combination of secretin and oxytocin administered in experiment CP-76 was therapeutically effective. It can been seen that there was a markedly higher level of C-fos immunoreactivity in the hypothalamus following induction of IBD (see the higher amount of dark immunostaining in the "IBD-experimental-untreated" slide as compared to the "IBD-control-untreated" slide). It can also bee seen that the amount of C-fos immunoreactivity in the hypothalamus was markedly lower in IBD rats that had been treated with a combination of secretin and oxytocin (see the lower amount of dark immunostaining in the "IBD-experimental-Secretin/Oxytocin Treatment" slide as compared to the "IBD-experimental-untreated" slide). As described in multiple locations in the above identified patent application, C-fos expression is a marker of the colitis-induced stress reaction.

9. **Exhibit C** shows yet another experiment in which a composition comprising a therapeutically effective amount of a combination of secretin and oxytocin was administered to rats prior to October 3, 2002. The first page of Exhibit C is a copy of a laboratory notebook page describing experiment "CP-77" which shows that in experiment CP-77 guts from the rats treated in experiment CP-76 (described in Exhibit B) were frozen. Pages 2-5 show of Exhibit C show that the combination of secretin and oxytocin administered in experiment CP-76 had a therapeutic effect in the gut (experiment CP-77). Gut tissues were stained with hemotoxylin and eosin in order to evaluate inflammation. Inflammation was observed in the mucosa and submucosa following the induction of IBD with TNBS (see the higher amount of neutrophils and macrophages in the mucosa and submucosa in the "Colon-IBD-Control-Untreated" slide as compared to the "Colon-IBD-Control-Treated" slide). There was markedly less inflammation in the guts of IBD rats that had been treated with a combination of secretin and oxytocin (see the lower amount of neutrophils and macrophages in the mucosa and submucosa in the "Colon-IBD-Control-Untreated" slide as compared to the "Colon-IBD-Control-Treated" slide).

10. We declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that the making of willfully false statements and the like is punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: July 20, 2009

Martha G. Welch

Date: July 19, 2009

David A. Ruggiero

Date: July 20, 2009

Muhammad Anwar